

# The Ratio of Blood Products Transfused Affects Mortality in Patients Receiving Massive Transfusions at a Combat Support Hospital

Matthew A. Borgman, MD, Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Thomas Repine, MD, Alec C. Beekley, MD, James Sebesta, MD, Donald Jenkins, MD, Charles E. Wade, PhD, and John B. Holcomb, MD

**Background:** Patients with severe traumatic injuries often present with coagulopathy and require massive transfusion. The risk of death from hemorrhagic shock increases in this population. To treat the coagulopathy of trauma, some have suggested early, aggressive correction using a 1:1 ratio of plasma to red blood cell (RBC) units.

**Methods:** We performed a retrospective chart review of 246 patients at a US Army combat support hospital, each of who received a massive transfusion ( $\geq 10$  units of RBCs in 24 hours). Three groups of patients were constructed according to the plasma to RBC ratio transfused dur-

ing massive transfusion. Mortality rates and the cause of death were compared among groups.

**Results:** For the low ratio group the plasma to RBC median ratio was 1:8 (interquartile range, 0:12–1:5), for the medium ratio group, 1:2.5 (interquartile range, 1:3.0–1:2.3), and for the high ratio group, 1:1.4 (interquartile range, 1:1.7–1:1.2) ( $p < 0.001$ ). Median Injury Severity Score (ISS) was 18 for all groups (interquartile range, 14–25). For low, medium, and high plasma to RBC ratios, overall mortality rates were 65%, 34%, and 19%, ( $p < 0.001$ ); and hemorrhage mortality rates were 92.5%, 78%, and 37%,

respectively, ( $p < 0.001$ ). Upon logistic regression, plasma to RBC ratio was independently associated with survival (odds ratio 8.6, 95% confidence interval 2.1–35.2).

**Conclusions:** In patients with combat-related trauma requiring massive transfusion, a high 1:1.4 plasma to RBC ratio is independently associated with improved survival to hospital discharge, primarily by decreasing death from hemorrhage. For practical purposes, massive transfusion protocols should utilize a 1:1 ratio of plasma to RBCs for all patients who are hypocoagulable with traumatic injuries.

**Key Words:** Blood components, Fresh frozen plasma, Trauma, Coagulopathy.

*J Trauma.* 2007;63:805–813.

**M**assive transfusion is defined as the transfusion of 10 or more red blood cell (RBC) units in a 24-hour period.<sup>1–3</sup> In civilian trauma centers, the incidence of patients with traumatic injuries receiving massive transfusion ranges between 1% and 3%,<sup>3–5</sup> with an incidence reported as high as 15% in patients with the most severe injuries.<sup>6</sup> Mortality rates for massive transfusion patients ranges between 20% and 50%.<sup>1,6,7</sup> Currently, 5% of all patients admitted to US combat support hospitals in Iraq require massive transfusions. Mortality rates among these patients is more than 30%.<sup>8</sup> The high risk of mortality in massive transfusion patients largely results from the “lethal triad” or “bloody vicious cycle” characterized by hypothermia, metabolic acidosis, and coagulopathy.<sup>9–12</sup> In approximately 30% of patients who have received a blood transfusion, coagulopathy results directly from the trauma itself. These patients present in the hypocoagulable state known as the coagulopathy of trauma.<sup>13</sup> The coagulopathy of trauma is multifactorial; it is consumptive because of widespread tissue trauma, is aug-

mented by dilution of hemostatic factors from crystalloid, colloid, and component therapy resuscitation, and exacerbated by hemorrhagic shock, metabolic acidosis, hypothermia, hyperfibrinolysis, hypocalcemia, and anemia.<sup>11,14–19</sup> Alternatively, coagulopathy can develop independent of acidosis and hypothermia secondary to trauma.<sup>20</sup>

Historically, whole blood was commonly used for patients suffering massive trauma.<sup>21,22</sup> By the late 1980s, however, component therapy had almost completely replaced whole blood therapy.<sup>23</sup> The primary purpose of component therapy was to improve resource utilization and reduce infectious disease transmission. This was accomplished by replacing blood component deficiencies individually based upon rigorous laboratory analysis. This approach of replacing specific hematologic deficits based upon laboratory analysis extended into the guidelines developed for patients requiring massive transfusion after injury. However, proof of the efficacy of this change in practice was lacking. Current transfusion recommendations were extrapolated from the setting of elective surgery, and may not be applicable to patients with severe trauma who are hypocoagulable, acidotic, and in hemorrhagic shock. Recently, published reports now recommend a 1:1:1 ratio (i.e. equal parts RBCs, fresh frozen plasma [FFP], and platelets) for component therapy based on a more physiologic regimen and is more similar to the composition of whole blood.<sup>1,15,24–28</sup> These recommendations, however,

Submitted for publication January 24, 2007.

Accepted for publication May 25, 2007.

Copyright © 2007 by Lippincott Williams & Wilkins

From Brooke Army Medical Center, Fort Sam Houston, TX.

Address for reprints: Matthew A Borgman, MD, 3851 Roger Brooke Drive, San Antonio, TX 78234; email: mattborgman@hotmail.com.

DOI: 10.1097/TA.0b013e3181271ba3

Report Documentation Page				Form Approved OMB No. 0704-0188	
Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.					
1. REPORT DATE <b>JAN 2007</b>		2. REPORT TYPE		3. DATES COVERED <b>00-00-2007 to 00-00-2007</b>	
4. TITLE AND SUBTITLE <b>The Ratio of Blood Products Transfused Affects Mortality in Patients Receiving Massive Transfusions at a Combat Support Hospital</b>				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S)				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) <b>Brooke Army Medical Center,Fort Sam Houston ,TX,78234</b>				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT <b>Approved for public release; distribution unlimited</b>					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT <b>Same as Report (SAR)</b>	18. NUMBER OF PAGES <b>9</b>	19a. NAME OF RESPONSIBLE PERSON
a. REPORT <b>unclassified</b>	b. ABSTRACT <b>unclassified</b>	c. THIS PAGE <b>unclassified</b>			

have been based on anecdotal evidence and not on outcome studies examining the effect of blood product transfusion ratios for trauma patients requiring massive transfusion.

Most deaths (80% to 85%) that occur during combat are not preventable. Sixty-six to 80% of the 15% to 20% of potentially survivable combat-related deaths are a result of hemorrhagic shock.<sup>27,29</sup> Scoring systems and predictive models that are able to rapidly identify who is at risk for massive transfusion have been recently published.<sup>30,31</sup> Expeditious recognition and treatment of coagulopathy is important because most patients requiring massive transfusion die within 6 hours of admission.<sup>30</sup> Resuscitation strategies that rapidly identify risk of massive transfusion and quickly address the coagulopathy of trauma should prevent deaths from uncontrolled hemorrhage and improve survival of potentially preventable deaths on the battlefield. Our objective in this retrospective study of patients with severe traumatic injuries requiring massive transfusion at a combat support hospital was to determine whether the ratio of plasma to RBCs transfused would affect survival by decreasing death from hemorrhage.

## METHODS

The data presented here were obtained under a human use protocol that the Institutional Review Board at Brooke Army Medical Center in San Antonio, TX approved. Using the Joint Theater Trauma Registry (JTTR) maintained at the US Army Institute of Surgical Research (USAISR) at Ft. Sam Houston in San Antonio, TX, we performed a retrospective analysis of data for trauma patients admitted to a combat support hospital (CSH) in Iraq between November 2003 and September 2005. The JTTR database was established by the Department of Defense to capture data prospectively from multiple nonintegrated clinical and administrative systems. This database provides comprehensive data collection from the point of injury through discharge from military treatment facilities for non-US military patients and from point of injury through rehabilitation for US patients. Non-US military patients are defined to include coalition soldiers and foreign national patients.

The JTTR was queried for patients who received a massive transfusion, defined as 10 or more RBC units (including both stored RBC and fresh whole blood units) in 24 hours from admission. Data analyzed from the JTTR in this study were Injury Severity Score (ISS), Abbreviated Injury Scale (AIS) scores, primary cause of death, time of death, mortality at hospital discharge, laboratory values, and vital signs at admission to the CSH, (hemoglobin, platelet level, base deficit, International Normalized Ratio [INR], systolic blood pressure, temperature, heart rate), and total crystalloid and blood products (RBC, FFP, cryoprecipitate, recombinant FVIIa [rFVIIa], apheresis platelet [aPLT], and fresh whole blood [FWB] units) administered within 24 hours from admission to the combat support hospital. Because 1 unit of FWB has approximately 1 unit of RBCs, plasma, and plate-

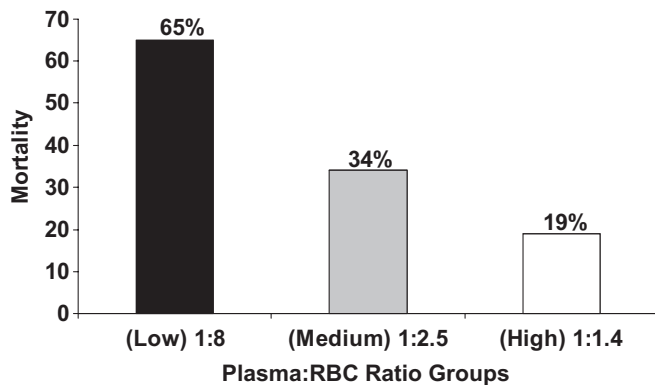
lets, the amount of RBC units transfused was calculated as the number of both stored RBC and FWB units transfused and plasma as FFP plus FWB units. One apheresis platelet unit is equal in number to approximately 6 to 10 units of leukocyte-reduced platelets.<sup>32</sup> The platelet contribution from FWB was not included in the calculation of apheresis platelet units transfused, though FWB has previously been shown to be as effective as 10 units of platelet concentrate.<sup>33</sup> The initial 24-hour amount of crystalloid and blood products transfused was also calculated as liters or units per hour. The rate of crystalloid and blood products per hour was calculated to adjust for the amount of crystalloid and blood products transfused to patients who died less than 24 hours from the initiation of the massive transfusion.

One investigator reviewed each patient's chart or autopsy results to record all injuries, from which the AIS score and ISS were calculated.<sup>34</sup> Primary outcome for all patients in this study was hospital discharge or overall mortality. For US military patients, this was tracked throughout all levels of care, including discharge from acute care hospitals in the United States. For non-US military patients, mortality was tracked until discharge from the CSH in Baghdad. Non-US military patients were not discharged or transferred until their surgical repair was stable, were not hemodynamically compromised, and did not require vasoactive agents or mechanical ventilation. The length of stay from admission to hospital discharge for both groups was measured. Time to death was defined as the time, in hours, from hospital admission to the time of death. For patients who had two mechanisms of death listed, a 0.5 was used for each in the calculation of the percentage of cause of death in each ratio group.

To analyze the effect of plasma to RBC ratios on mortality, patients were divided into groups based on the ratio of plasma to RBC units transfused. Three separate groups of patients were identified based on a "bootstrapping" technique that combined groups of patients that had similar mortality rates based upon the plasma to RBC ratios transfused to individual patients. With use of this method, the six groups of ratios that were initially constructed were combined to three groups. The plasma to RBC ratio was the number of plasma units divided by the RBC units transfused in the first 24 hours of care at the CSH.

Subpopulations were also analyzed to determine whether injury location affected the relationship between mortality and the ratio of plasma to RBCs transfused. To determine the effect of thoracic and head trauma in relationship to the plasma to RBC ratio and mortality, additional analyses were performed with and without patients who had thoracic or head and neck AIS scores of 4 or 5. The plasma to RBC ratio was also analyzed without the addition of FWB in the ratio, as well as without patients who were treated with rFVIIa.

All variables collected were analyzed to determine which were associated with overall mortality. Logistic regression was then used to determine independent associations between variables measured and overall mortality. The logistic regres-



**Fig. 1.** Percentage mortality associated with low, medium, and high plasma to RBC ratios transfused at admission. Ratios are median ratios per group and include units of fresh whole blood counted both as plasma and RBCs.

sion model initially used all variables associated with mortality with a  $p$  value  $<0.2$ . Variables were removed if significant colinearity was measured by Pearson's correlation coefficient or variance inflation.

All continuous nonparametric data are described as median (interquartile range) or median (interquartile range) [mean] if the median value is zero. Mann-Whitney  $U$  test and Kruskal Wallis tests were used for comparisons of continuous data. All categorical data were compared with  $\chi^2$  or Fisher's exact test as appropriate. Statistical analysis was performed with SPSS 14.0 (Chicago, IL). Significant differences were determined at  $p < 0.05$ .

## RESULTS

Between November 2003 and September 2005, 5,293 patients were admitted to the CSH in Baghdad. The JTTR identified 246 (4.6%) patients who received massive transfusion. Penetrating injuries occurred in 232 of 246 (94%) of these patients. Three patients were female. The median age of the patients studied was 24 years (interquartile range, 21–30). The median ISS was 18 (interquartile range, 16–25). The combat support hospital length of stay for patients was a median of 2 (1–6) days. The median time from admission to the CSH to evacuation to Germany for US patients was 1 day (1–2 days). The overall mortality was 28%. Median plasma to RBC transfusion ratios for survivors versus nonsurvivors were 1:1.6 (1:1.3–1:2.2) and 1:2.3 (1:1.4–1:5.1), respectively ( $p < 0.001$ ). Median plasma to RBC ratios were 1:8, 1:2.5, and 1:1.4, and are defined as low, medium, and high ratios respectively, ( $p < 0.001$ ). The low, medium, and high ratio groups had plasma to RBC ratio ranges of 0:22–1:4, 1:3.9–1:2.1, and 1:2–1:0.6, respectively. As the ratio of plasma to RBC increased, mortality significantly decreased (Fig. 1). The mortality of low, medium, and high groups were 65%, 34%, and 19%, respectively ( $p < 0.001$ ).

Descriptive statistics for severity of injury, admission vital signs, and laboratory values for the three groups are in

Table 1. Severe (AIS scores of 4 and 5) thoracic injuries were more common in the low ratio group compared with in the medium and high groups. All vital signs and laboratory results were comparable, except for hemoglobin, which was significantly lower in the low ratio group compared with in the medium and high groups.

In the first 24 hours of admission, the rate per hour of crystalloid and RBC units administered was less in the high ratio group compared with in the medium and low groups (Table 2). The total amount and rate per hour of plasma as well as the rate per hour of FWB was higher in the medium and high ratio groups ( $p < 0.001$ ). The low ratio group did not receive aPLTs, which were only used in 27% of patients. Cryoprecipitate was used more in the high ratio group ( $p < 0.01$ ), though given at a higher rate in the medium and low ratio groups ( $p < 0.001$ ) and was only used in 51% of the patient population (Table 2).

Nonsurvivors in the low and medium ratio groups died significantly sooner than those in the high ratio group (Fig. 2). Median time of death measured in hours from admission to the hospital was 2 hours (interquartile range, 1–4) in the low group and 4 hours (interquartile range, 2–16) in the medium group, compared with 38 hours (interquartile range, 4–155) in the high ratio group ( $p < 0.001$ ).

The relationship between plasma to RBC ratios transfused and overall mortality remained in the alternative analyses performed. Differences in mortality remained significant in the high, compared with in the low, ratio group when patients with thoracic and head trauma were individually removed from the analysis (Table 3). The relationship between plasma to RBC ratios transfused and overall mortality also remained when only stored FFP and RBCs (FWB units not included) were used to calculate the ratio, as well as when patients who were treated with rFVIIa were excluded (Table 3).

Table 4 indicates that many of the admission vital signs, laboratory values, and Injury Severity Scores, in addition to the ratio of plasma to RBCs, were associated with overall mortality. Table 5 reveals that the plasma to RBC ratio was independently associated with overall survival (odds ratio 8.6, 95% confidence interval 2.1–35.2) and that both base deficit and AIS for head and neck were independently associated with decreased overall survival upon logistic regression.

Figure 2 displays the primary causes of death in each ratio group. The percentage of deaths from hemorrhage was lower in the high ratio group (11.5 of 31; 37%), compared with in the low ratio group (18.5 of 20; 92.5%) ( $p < 0.001$ ). This represents an absolute reduction of 55% and a relative reduction of 60%. There were fewer hemorrhagic deaths in the high ratio group compared with in the medium ratio group ( $p < 0.05$ ). Likely reflecting the increased survival time, multiorgan failure deaths were more frequent in the high ratio group compared with in the low ratio group.

**Table 1** Descriptive Statistics for Each Plasma to RBC Ratio Group

Variable Median (IQR)	Low Ratio Group,* n = 31 1:8 (0.12–1.5)	Medium Ratio Group, n = 53 1:2.5 (1.3.0–1:2.3)	High Ratio Group, n = 162 1:1.4 (1.1.7–1:1.2)
ISS†	18 (16–25)	17 (13–25)	18 (16–25)
ISS >25 (%)	23	21	22
AIS score (% 4 or 5)			
Head/neck	16	6	10
Face	0	0	0.6
Thorax§	26 <sup>a</sup>	9 <sup>ab</sup>	7 <sup>b</sup>
Abdomen	26	23	27
Pelvis/extremity	19	23	28
% penetrating trauma	94	92	95
% blunt trauma	6	8	5
INR, n = 212	1.78 (1.00–2.86), n = 21	1.57 (1.31–2.10), n = 42	1.54 (1.30–2.20), n = 149
Hgb,† n = 234	9.4 (7.1–11.1), n = 27 <sup>a</sup>	10.8 (8.5–12.7), n = 48 <sup>ab</sup>	10.9 (9.1–13.1), n = 159 <sup>b</sup>
Plt concentration, n = 174	225 (120–281), n = 14	177 (128–241), n = 33	218 (154–278), n = 127
Base deficit, n = 201	13 (4–14), n = 22	9 (3–14), n = 42	8 (4–13), n = 137
Temperature (°F), n = 195	97 (94.9–97.6), n = 18	96.2 (94.1–98.0), n = 45	95.9 (94.0–97.3), n = 132
Heart rate, n = 233	122 (97–149), n = 29	118 (104–133), n = 51	111 (90–128), n = 153
SBP, n = 231	90 (80–106), n = 29	98 (74–116), n = 49	97 (80–122), n = 153

Values with different superscripts (<sup>a</sup>, <sup>b</sup>, <sup>c</sup>) are significantly different ( $p < 0.05$ ).

\* Ratio calculated as (FFP + FWB):(RBC + FWB).

† Data presented as median (interquartile range).

‡ Mann-Whitney  $U$  test.

§ Chi Square test.

ISS, Injury Severity Score; AIS, Abbreviated Injury Scale; INR, international normalized ratio; Hgb, hemoglobin (mg/dL); Plt concentration, platelet level  $\times 1,000/\mu\text{L}$ ; SBP, systolic blood pressure.

**Table 2** Crystalloid and Blood Products for Each Plasma to RBC Ratio Group

Variable Median (IQR)	Low Ratio Group,* n = 31 1:8 (0.22–1.5)	Medium Ratio Group, n = 53 1:2.5 (1.3.0–1:2.3)	High Ratio Group, n = 162 1:1.4 (1.1.7–1:1.2)
Crystalloid (L)†§	7.0 (2.0–9.6) <sup>a</sup>	8.0 (4.4–11.5) <sup>ab</sup>	9.6 (6.0–12.9) <sup>b</sup>
Crystalloid (L/h)§	1.8 (0.36–4.2) <sup>a</sup>	0.6 (0.3–1.5) <sup>ab</sup>	0.5 (0.4–0.7) <sup>b</sup>
RBC	16 (12–18)	16 (12–26)	17 (12–24)
RBC/h§	4 (0.5–11.8) <sup>a</sup>	0.9 (0.6–4.0) <sup>ab</sup>	0.8 (0.6–1.3) <sup>b</sup>
FWB	0 (0–0) [0.1]	0 (0–2) [1.1]	0 (0–4) [3.1]
FWB/h§	0 (0–0) [0.01] <sup>a</sup>	0 (0–0.1) [0.15] <sup>b</sup>	0 (0–0.2) [0.23] <sup>c</sup>
Plasma§	2 (0–3) <sup>a</sup>	6 (4–10) <sup>b</sup>	12 (9–18) <sup>c</sup>
Plasma/h§	0.1 (0–0.4) [0.57] <sup>a</sup>	0.3 (0.2–1.4) [1.1] <sup>b</sup>	0.6 (0.4–1.0) [1.1] <sup>c</sup>
aPLT§	None received <sup>a</sup>	0 (0–0) [0.4] <sup>b</sup>	0 (0–1) [0.8] <sup>c</sup>
aPLT/h§	None received <sup>a</sup>	0 (0–0) [0.02] <sup>ab</sup>	0 (0–0) [0.05] <sup>b</sup>
Cryoprecipitate§	0 (0–0) [1.6] <sup>a</sup>	0 (0–10) [6.6] <sup>b</sup>	9 (0–10) [9.1] <sup>b</sup>
Cryoprecipitate/h§	0 (0–0) [0.7] <sup>a</sup>	0 (0–1.3) [0.9] <sup>b</sup>	0.4 (0–0.8) [0.6] <sup>b</sup>
rFVIIa use‡	16% <sup>a</sup>	26% <sup>ab</sup>	38% <sup>b</sup>

\* Ratio calculated as (FFP + FWB):(RBC + FWB).

† Data presented as median (interquartile range) with or without [mean].

‡ Data presented as percentage used in each cohort (ie rFVIIa use/total number in cohort).

§ Mann-Whitney  $U$  test.

Values with different superscripts (<sup>a</sup>, <sup>b</sup>, <sup>c</sup>) are significantly different ( $p < 0.05$ ).

Crystalloid, liters normal saline and Lactated Ringers; RBC, units packed red blood cells and fresh whole blood; FWB, units fresh whole blood; Plasma, units fresh frozen plasma and fresh whole blood; aPLT, apheresis platelet units; rFVIIa, recombinant Factor VIIa.

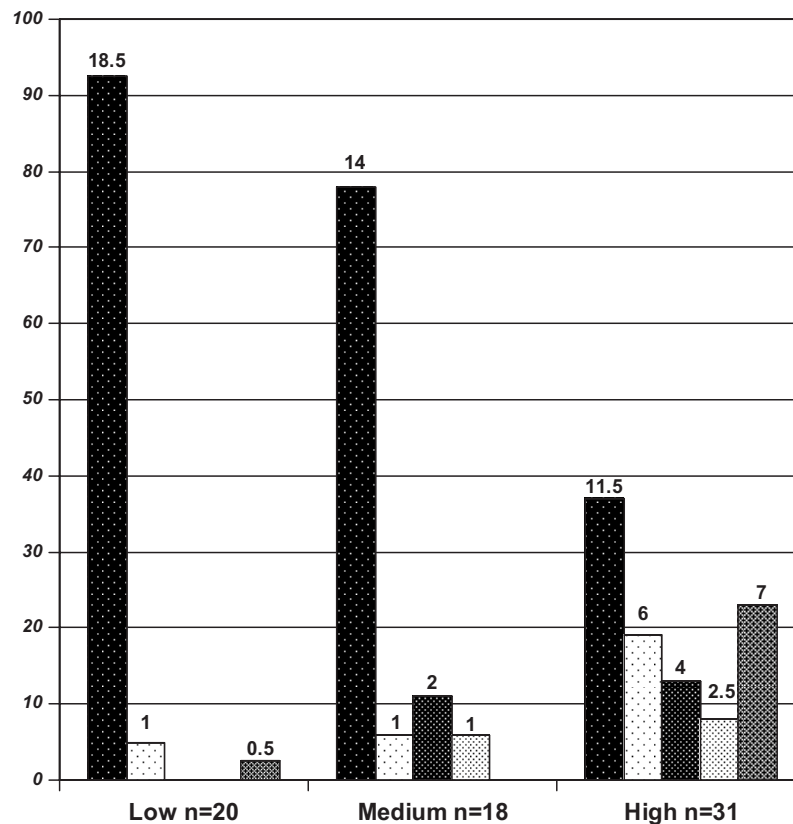
## DISCUSSION

Our results indicate that for patients with significant traumatic injuries requiring massive transfusion, a higher plasma to RBC ratio is independently associated with improved survival, primarily decreasing early (<4 hours from admission) death from hemorrhage. The patients with the lowest mortality rate in our study were transfused a median plasma to RBC ratio of

1:1.4. This study supports recent reports in the literature that have called for the increased transfusion of coagulation factors for patients requiring massive transfusion<sup>1,15,25,26,35,36</sup> and that have raised concerns about the increased use of RBCs and crystalloids in critically ill patients.<sup>26,35,37–50</sup>

Earlier massive transfusion protocols developed for patients bleeding a large amount of whole blood, did not replace





<b>Hemorrhage %†</b>	<b>92.5<sup>a</sup></b>	<b>78<sup>a</sup></b>	<b>37<sup>b</sup></b>
<b>Sepsis %</b>	<b>5</b>	<b>6</b>	<b>19</b>
<b>MOF %</b>	<b>0</b>	<b>11</b>	<b>13</b>
<b>Airway/Breathing %</b>	<b>0</b>	<b>6</b>	<b>8</b>
<b>CNS %</b>	<b>2.5</b>	<b>0</b>	<b>23</b>
<b>Time to death (hrs)<sup>2*</sup></b>	<b>2 (1 – 4)<sup>a</sup></b>	<b>4 (2-16)<sup>b</sup></b>	<b>38 (4 – 155)<sup>c</sup></b>

**Fig. 2.** Comparison of the number and percentage of the primary cause of death for all of the deaths in each plasma to RBC ratio group. Number on column represents absolute number that died from each cause listed. When two causes were listed for a patient, they were counted as 0.5. <sup>2</sup>Data presented in hours as median (interquartile range); \*Mann-Whitney U test; †Chi Square test. Values with different superscripts (<sup>a</sup>, <sup>b</sup>, <sup>c</sup>) are significantly different ( $p < 0.05$ ).

**Table 3** Comparison of Mortality Rates of Alternative Patient Cohorts and Plasma to RBC Ratios

Plasma to RBC Ratio (Range)	Low Ratio (0:22–1:4)	Medium Ratio (1:3.9–1:2.1)	High Ratio (1:2–1:0.59)
Primary analysis*	65% <sup>a</sup> n = 31	34% <sup>b</sup> n = 53	19% <sup>c</sup> n = 162
Excluding thoracic trauma	57% <sup>a</sup> n = 23	29% <sup>b</sup> n = 48	19% <sup>b</sup> n = 152
Excluding neurotrauma	62% <sup>a</sup> n = 26	36% <sup>b</sup> n = 50	15% <sup>c</sup> n = 145
Excluding whole blood†	66% <sup>a</sup> n = 38	27% <sup>b</sup> n = 59	19% <sup>b</sup> n = 149
Excluding rFVIIa	69% <sup>a</sup> n = 26	38% <sup>b</sup> n = 39	15% <sup>c</sup> n = 100

Values with different superscripts (<sup>a</sup>, <sup>b</sup>, <sup>c</sup>) are significantly different ( $p < 0.05$ ) (Chi Square Test).

\* See Methods Section.

† Ratio calculated as FFP:RBC units.

whole blood, but rather called for a much greater percentage of RBC units.<sup>35</sup> Such protocols recommended that FFP only be transfused if prothrombin time (PT) or partial thrombo-

plastin time (PTT) was 1.5 times normal, or after 10 RBC units were transfused. Additionally, these massive transfusion protocols called for 1 unit of FFP to be given for every 4 to

**Table 4** Analysis of Data Associated With Mortality

Variable	Survivors	Nonsurvivors	p Value
AIS head/neck score, % 4 or 5 (n = 245)	7	19	0.005 <sup>†</sup>
AIS face score, % 4 or 5 (n = 245)	0	1.4	0.11 <sup>†</sup>
AIS external score, % 4 or 5 (n = 245)	0.5	0	0.53 <sup>†</sup>
AIS pelvis/extremity score, % 4 or 5 (n = 246)	28	19	0.13 <sup>†</sup>
AIS abdomen score, % 4 or 5 (n = 245)	22	36	0.024 <sup>†</sup>
AIS thorax score, % 4 or 5 (n = 245)	6	20	0.011 <sup>†</sup>
ISS (n = 246)	17 (13–25)	25 (17–29)	<0.001*
Systolic blood pressure (n = 231)	98 (80–120)	90 (70–109)	0.024*
Heart rate (n = 233)	112 (91–132)	121 (100–140)	0.052*
Temperature (n = 195)	96.1 (94.4–97.7)	94.9 (93.2–97.3)	0.049*
Base deficit (n = 201)	7 (3–12)	13 (8–18)	<0.001*
INR (n = 212)	1.5 (1.2–1.8)	2.1 (1.6–3.4)	<0.001*
Platelet level (n = 174)	222 (152–278)	175 (118–234)	0.015*
Hemoglobin (n = 234)	11.1 (9.0–13)	9.9 (7.2–11.5)	0.003*
% rFVIIa use (n = 246)	34	30	0.44 <sup>†</sup>
Plasma:RBC ratio (n = 246)	1:1.6 (1:1.3–1:2.2)	1:2.3 (1:1.4–1:5.1)	<0.001*

n = number of patients with data available.

\* Mann-Whitney *U* test.

<sup>†</sup> Chi Square test.

AIS, Abbreviated Injury Scale; ISS, Injury Severity Score; rFVIIa, recombinant Factor VIIa.

10 RBC units and platelets to be infused at less than 50,000 to 100,000.<sup>35,52,53</sup>

The standard clinical practice guidelines for optimally diagnosing and treating seriously injured casualties are based on expert opinion and theoretical assumptions rather than robust laboratory or clinical data.<sup>35,52,54</sup> Furthermore, they have frequently been extrapolated from elective operative settings, and may not be applicable to the patient with severe trauma who is in a hypocoagulable state and in hemorrhagic shock. Given these concerns, there has been recent controversy in the approach to patients requiring massive transfusions after injury.

Several current clinical practice guidelines have called for a strategy of aggressive early correction of coagulation factors in a 1:1:1 ratio (i.e., plasma:RBC:platelets) in patients with severe trauma or requiring massive transfusions.<sup>1,25</sup> These recommendations are echoed in a clinical practice guideline instituted in September 2004 at US combat hospitals, which support the early use of a 1:1:1 ratio of plasma to RBC to platelets for patients at high risk of requiring a massive transfusion based upon clinical or laboratory data. The majority of these recommendations are based upon ex-

pert opinion or computer modeling. This study is the first to support, with comparative ratio data in three equally injured groups of patients and regression analysis, the concept that early and aggressive replacement of coagulation factors may improve survival by decreasing death from hemorrhage for patients requiring massive transfusions based on data from a large population with traumatic injuries. Interestingly, our results support a report by Hirshberg et al. that used a computer simulation model and found that a plasma to RBC ratio of 2:3 was necessary to effectively minimize coagulopathy in exsanguinating hemorrhage.<sup>55</sup>

Previous reports of the outcomes of patients requiring massive transfusion have documented similar results in smaller populations. Lucas and Ledgerwood found that coagulopathy was exacerbated in several studies in which trauma patients were transfused less plasma relative to RBCs.<sup>53,54</sup> Cinat et al., in a study of 45 massively transfused patients reported the plasma to RBC ratio for survivors was 1:1.8 compared with 1:2.5 in nonsurvivors ( $p = 0.06$ ).<sup>57</sup> Cosgriff et al. in a prospective cohort of 56 massive transfusion patients found significant coagulopathy in 47% of patients, predicted by persistent hypothermia and progressive metabolic acidosis.<sup>10</sup> Several other retrospective studies have confirmed the presence of coagulopathy in patients requiring massive transfusion<sup>31</sup> and have called for increased use of coagulation factors.<sup>2,14,17,44,58,59</sup>

There was an absolute and relative reduction in mortality of 55% and 60%, respectively, in the high (1:1.4) plasma to RBC ratio group compared with in the low (1:8) plasma to RBC ratio group. The correction of the coagulopathy of trauma must begin early, before the patient enters the “bloody vicious cycle”. Our results reinforced this approach, as those in the low plasma to RBC ratio group died from uncontrolled

**Table 5** Odds Ratio Predicting Survival Using Multivariate Logistic Regression

Variable	Odds Ratio (95% CI)	p Value
Plasma:RBC ratio	8.6 (2.1–35)	0.003
AIS head/neck score	0.76 (0.61–0.94)	0.013
AIS thorax score	0.73 (0.57–0.92)	0.009
Systolic blood pressure	1.0 (0.98–1.01)	0.457
Hemoglobin	1.1 (0.91–1.2)	0.501
Base deficit	0.89 (0.84–0.95)	<0.001

AIS, Abbreviated Injury Scale.

hemorrhage within a median of 2 hours. Other studies have demonstrated that the coagulopathy of trauma occurs early in patients with severe trauma and that the severity of coagulopathy is associated with mortality.<sup>10,11,14,58,60,61</sup> Early and appropriate use of plasma in the high ratio group likely prevented the start of this cycle. Gonzalez et al. have recently elegantly demonstrated that trauma patients who arrive in the intensive care unit with a persistent coagulopathy have increased mortality rates and they recommend earlier and more aggressive use of plasma.<sup>36</sup>

Our population of patients also received an increased amount of aPLT and cryoprecipitate. One apheresis platelet unit usually also contains 250 to 350 mL of plasma. This increased use of plasma, in addition to platelets and cryoprecipitate, supports the concept of damage control or hemostatic resuscitation.<sup>15,26,28</sup> This approach emphasizes the aggressive diagnosis and treatment of coagulopathy in patients at high risk of requiring massive transfusion before it occurs or early in the resuscitation. If successful it will prevent and treat the lethal triad of trauma, which includes the early coagulopathy of trauma, from occurring.<sup>15,18,28,62</sup> Similar in philosophical approach to damage control surgery the concept is to “stay out of trouble rather than get out of trouble”.

Our results indicate that the rate per hour of crystalloid and blood products was decreased with higher plasma to RBC ratios. We hypothesize that the early, increased use of plasma in these severely injured patients helped control the coagulopathy of trauma more efficiently, and, as a result required less crystalloid and RBCs per hour during the first 24 hours of resuscitation. Additionally, the use of plasma instead of crystalloids and RBCs helped prevent or limit the development of dilutional coagulopathy.<sup>15</sup> Conversely, we believe that patients who received less plasma and more crystalloid and RBCs in the low and medium plasma to RBC ratio groups entered the “bloody vicious cycle”, and died significantly sooner from uncontrolled hemorrhagic shock. The rate of blood products and crystalloid may have also been reduced for the survivors in the high plasma to RBC ratio group as a result of not requiring active resuscitation during the entire 24 hours after initiating a massive transfusion. We suspect that both improved hemostasis and survival, and the lack of need to be actively resuscitated contributed to the decreased rate of products and crystalloid transfused in the high plasma to RBC ratio group.

Patients who received low or medium plasma to RBC ratios died predominantly of hemorrhage at a median of 2 to 4 hours. This supports the concept that patients who require massive transfusion are at risk of early (<6 hours from admission) death from hemorrhage,<sup>30</sup> and indicates rapid treatment of coagulopathy with a higher ratio of plasma to RBC prevents early death from hemorrhage. This was evidenced by the median time to death of 38 hours in the high ratio group. Patients who received high plasma to RBC ratios had a higher incidence of death from sepsis and multiorgan

failure versus hemorrhage as a result of surviving long enough to develop these complications. This is supported by the median time to death in the low and medium ratio groups compared with in the high ratio group. This relationship was noted in another similar study evaluating the effect of blood products on mortality.<sup>63</sup> Because of the retrospective nature of this study, we cannot rule out the possibility that the increased use of plasma, apheresis platelets, and cryoprecipitate may have contributed to these results, as has been previously reported.<sup>64</sup>

Our results are subject to limitations inherent in retrospective studies, including incomplete data collection, lack of standard timing for measuring variables, and lack of a massive transfusion protocol that was consistently applied to patients. The variable with the highest percentage of missing data was the admission platelet concentration at 30%. It is possible that the exclusion of these missing values may have affected our results, but because ISS and mechanism of injury were equal in all three groups, it is likely that there was a comparable degree of coagulopathy, as has been shown previously.<sup>14</sup> Another potential confounder is the possibility that the patients who did not receive plasma did not primarily as a function of dying before they had a chance to receive plasma. These patients may have been more critically ill than the others who were able to wait for plasma to be thawed. Although this is possible, all available indicators of severity of injury including ISS, systolic blood pressure, base deficit, and INR were equal between the three groups of patients which makes this potential confounder less likely.

Despite these limitations, this study is currently one of the largest reviews of patients with massive transfusion in trauma to analyze the effects of blood product transfusion and mortality. Additionally, we were able to adjust for many confounding variables in our regression analysis to include thoracic AIS values, admission hemoglobin concentrations, and rFVIIa use, which were each different in the low, medium, and high ratio groups that were compared. In addition to adjusting for thoracic AIS score in the regression model, we also analyzed the relationship between ratio of plasma to RBCs transfused with the exclusion of patients with severe thoracic injuries. In this analysis, the relationship of increased plasma to RBC ratio and decreased mortality remained between the low and high ratio groups (Table 3).

We believe that our results support the development of randomized controlled trials in animal and human subjects that will evaluate the effect of plasma to RBC ratios transfused to patients at risk of requiring massive transfusions. Ratios tested should also include plasma to RBC ratios of greater than 1:1 to evaluate if more plasma than RBCs would improve survival in coagulopathic patients with severe traumatic injury. Strategies that aggressively treat the coagulopathy of trauma and decrease the use of stored RBCs in patients with severe traumatic injuries including early and increased use of plasma, platelets, cryoprecipitate, or fresh whole blood if available, and the aggressive treatment of hypothermia,



metabolic acidosis, and hypocalcemia need continued study to determine whether they can improve outcomes.

One method that combat support hospitals and some large civilian trauma centers are currently using to facilitate early transfusion of increased plasma to RBC ratios is the use of thawed plasma. Thawed plasma is simply FFP, which after thawing, is kept refrigerated at 4°C for up to 5 days. This product is an American Association of Blood Banks (AABB) approved concept. Thawed AB plasma is stored at amounts equal to that of emergency release type O RBCs in emergency department refrigerators. This allows both blood products to be used immediately and concurrently upon presentation of a patient at risk for massive transfusion. Once thawed plasma is transfused it is immediately replaced by the blood bank to maintain availability for the next patient. Although thawed plasma was not used in the patients analyzed in this study, the results presented here have helped change our practice in the theater of operations and today thawed plasma is widely available at the busiest combat support hospitals, resulting in a decrease in plasma waste. Large civilian trauma centers should consider the use of thawed plasma to permit the transfusion of plasma to RBCs in a 1:1 ratio or at least in a 1:2 ratio at admission for patients with severe traumatic injuries who present with the coagulopathy of trauma.

Based upon these data the US Army Surgeon General has recently distributed a policy recommending that a 1:1 plasma to RBC ratio be transfused to all patients with significant trauma and who are at risk for requiring a massive transfusion.

## CONCLUSIONS

Recent literature demonstrates that the risk of requiring a massive transfusion can be rapidly identified and death from hemorrhage occurs quickly for patients with severe traumatic injuries requiring massive transfusion. The transfusion of plasma to RBCs in a 1:1 ratio is a rapid treatment that improves survival for patients at risk of hemorrhagic shock. We suggest that the empiric ratio of plasma to RBC should approximate 1:1 for patients with traumatic injuries requiring massive transfusions. Future prospective randomized controlled trials are needed to compare empiric plasma to RBC ratios for patients with severe traumatic injuries.

## REFERENCES

- Malone DL, Hess JR, Fingerhut A. Massive transfusion practices around the globe and a suggestion for a common massive transfusion protocol. *J Trauma*. 2006;60(Suppl):S91–S96.
- Phillips TF, Soulier G, Wilson RF. Outcome of massive transfusion exceeding two blood volumes in trauma and emergency surgery. *J Trauma*. 1987;27:903–910.
- Wudel JH, Morris JA Jr, Yates K, Wilson A, Bass SM. Massive transfusion: outcome in blunt trauma patients. *J Trauma*. 1991;31:1–7.
- Como JJ, Dutton RP, Scalea TM, Edelman BB, Hess JR. Blood transfusion rates in the care of acute trauma. *Transfusion*. 2004;44:809–813.
- Malone DL, Dunne J, Tracy JK, Putnam AT, Scalea TM, Napolitano LM. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. *J Trauma*. 2003;54:898–905; discussion 905–907.
- Huber-Wagner S, Qvick M, Mussack T, et al. Massive blood transfusion and outcome in 1062 polytrauma patients: a prospective study based on the Trauma Registry of the German Trauma Society. *Vox Sang*. 2007;92:69–78.
- Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: a reassessment. *J Trauma*. 1995;38:185–93.
- Perkins J, Schreiber M, Wade C, Holcomb J. Early versus late recombinant factor VIIa (rFVIIa) in combat trauma patients requiring massive transfusion. *J Trauma*. 2007;62:1095–1099; discussion 1099–1101.
- Engstrom M, Schott U, Romner B, Reinstrup P. Acidosis impairs the coagulation: a thromboelastographic study. *J Trauma*. 2006;61:624–628.
- Cosgriff N, Moore EE, Sauaia A, Kenny-Moynihan M, Burch JM, Galloway B. Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidosis revisited. *J Trauma*. 1997;42:857–861, discussion 861–862.
- DeLoughery TG. Coagulation defects in trauma patients: etiology, recognition, and therapy. *Crit Care Clin*. 2004;20:13–24.
- Ferrara A, MacArthur JD, Wright HK, Modlin IM, McMillen MA. Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion. *Am J Surg*. 1990;160:515–518.
- Kaufmann CR, Dwyer KM, Crews JD, Dols SJ, Trask AL. Usefulness of thromboelastography in assessment of trauma patient coagulation. *J Trauma*. 1997;42:716–720, discussion 720–722.
- Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. *J Trauma*. 2003;54:1127–1130.
- Hess JR, Holcomb JB, Hoyt DB. Damage control resuscitation: the need for specific blood products to treat the coagulopathy of trauma. *Transfusion*. 2006;46:685–686.
- Hess JR, Lawson JH. The coagulopathy of trauma versus disseminated intravascular coagulation. *J Trauma*. 2006;60(Suppl):S12–S19.
- Hewson JR, Neame PB, Kumar N, et al. Coagulopathy related to dilution and hypotension during massive transfusion. *Crit Care Med*. 1985;13:387–391.
- Martinowitz U, Michaelson M. Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: a report by the Israeli Multidisciplinary rFVIIa Task Force. *J Thromb Haemost*. 2005;3:640–648.
- Rohrer MJ, Natale AM. Effect of hypothermia on the coagulation cascade. *Crit Care Med*. 1992;20:1402–1405.
- Brohi K, Cohen MJ, Ganter MT, Matthay MA, Mackersie RC, Pittet J. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? *Ann Surg*. 2007;245:812–818.
- Coates JB. Blood Program in World War II. Washington, DC: Office of the Surgeon General, Dept. of the Army; United States Army Medical Service; 1964.
- Pfeffermann R, Rozin RR, Durst AL, Marin G. Modern war surgery: operations in an evacuation hospital during the October 1973 Arab-Israeli war. *J Trauma*. 1976;16:694–703.
- Repine TB, Perkins JG, Kauvar DS, Blackburne L. The use of fresh whole blood in massive transfusion. *J Trauma*. 2006;60(Suppl):S59–S69.
- Dutton RP, Carson JL. Indications for early red blood cell transfusion. *J Trauma*. 2006;60(Suppl):S35–S40.
- Ketchum L, Hess JR, Hiippala S. Indications for early fresh frozen plasma, cryoprecipitate, and platelet transfusion in trauma. *J Trauma*. 2006;60(Suppl):S51–S58.

26. Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma*. 2007;62:307–310.
27. Holcomb JB, McMullin N, Pearse L, et al. Causes of death in US Special Operations Forces in the Global War on Terrorism: 2001–2004. *Ann Surg*. 2007;245:986–991.
28. McMullin NR HJ, Sondeen J. Hemostatic resuscitation. In: Vincent J, ed. Yearbook of Intensive Care and Emergency Medicine. New York: Springer; 2006:265–278.
29. Bellamy RF. The causes of death in conventional land warfare: implications for combat casualty care research. *Mil Med*. 1984; 149:55–62.
30. Moore FA. Need for massive transfusion can be predicted early after trauma center arrival [abstract]. *J Trauma*. 2007;62:270.
31. Yucel N, Lefering R, Maegele M, et al. Trauma Associated Severe Hemorrhage (TASH)-Score: probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma. *J Trauma*. 2006;60:1228–1236, discussion 1236–1237.
32. Drews RE. Critical issues in hematology: anemia, thrombocytopenia, coagulopathy, and blood product transfusions in critically ill patients. *Clin Chest Med*. 2003;24:607–622.
33. Mohr R, Martinowitz U, Lavee J, Amroch D, Ramot B, Goor DA. The hemostatic effect of transfusing fresh whole blood versus platelet concentrates after cardiac operations. *J Thorac Cardiovasc Surg*. 1988;96:530–534.
34. Watts DD, Trask A, Soeken K, Perdue P, Dols S, Kaufmann C. Hypothermic coagulopathy in trauma: effect of varying levels of hypothermia on enzyme speed, platelet function, and fibrinolytic activity. *J Trauma*. 1998;44:846–854.
35. Ho AM, Karmakar MK, Dion PW. Are we giving enough coagulation factors during major trauma resuscitation? *Am J Surg*. 2005;190:479–484.
36. Gonzalez EA, Moore FA, Holcomb JB, et al. Fresh frozen plasma should be given earlier to patients requiring massive transfusion. *J Trauma*. 2007;62:112–119.
37. Basran S, Frumento RJ, Cohen A, et al. The association between duration of storage of transfused red blood cells and morbidity and mortality after reoperative cardiac surgery. *Anesth Analg*. 2006;103:15–20.
38. Hebert PC, Fergusson DA, Stather D, et al. Revisiting transfusion practices in critically ill patients. *Crit Care Med*. 2005;33:7–12, discussion 232–233.
39. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340:409–417.
40. Ho J, Sibbald WJ, Chin-Yee IH. Effects of storage on efficacy of red cell transfusion: when is it not safe? *Crit Care Med*. 2003; 31(Suppl):S687–S697.
41. Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA*. 1993;269:3024–3029.
42. Napolitano LM, Corwin HL. Efficacy of red blood cell transfusion in the critically ill. *Crit Care Clin*. 2004;20:255–268.
43. Zallen G, Offner PJ, Moore EE, et al. Age of transfused blood is an independent risk factor for postinjury multiple organ failure. *Am J Surg*. 1999;178:570–572.
44. Harvey MP, Greenfield TP, Sugrue ME, Rosenfeld D. Massive blood transfusion in a tertiary referral hospital. Clinical outcomes and haemostatic complications. *Med J Aust*. 1995;163:356–359.
45. McIntyre LA, Hebert PC. Can we safely restrict transfusion in trauma patients? *Curr Opin Crit Care*. 2006;12:575–583.
46. Tinmouth A, Fergusson D, Yee IC, Hebert PC. Clinical consequences of red cell storage in the critically ill. *Transfusion*. 2006;46:2014–2027.
47. Alam HB, Rhee P. New developments in fluid resuscitation. *Surg Clin North Am*. 2007;87:55–72, vi.
48. Hoyt DB. Fluid resuscitation: the target from an analysis of trauma systems and patient survival. *J Trauma*. 2003;54(Suppl): S31–S35.
49. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354:2564–2575.
50. Cotton BA, Guy JS, Morris JA Jr, Abumrad NN. The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. *Shock*. 2006;26:115–121.
51. Spinella PC, Perkins JG, Grathwohl KW, et al, and the 31st CSH Research Working Group. The risks associated with fresh whole blood and red blood cell transfusions in a combat support hospital. *Crit Care Med*. 2007;(in press).
52. Robb WJ. Massive transfusion in trauma. *AACN Clin Issues*. 1999; 10:69–84, quiz 138–140.
53. Ledgerwood AM, Lucas CE. A review of studies on the effects of hemorrhagic shock and resuscitation on the coagulation profile. *J Trauma*. 2003;54(Suppl):S68–S74.
54. Montenegro L, Jobes D. Complications of massive transfusion. In: Atlee JL, ed. Complications in Anesthesia. Philadelphia: Elsevier/ Saunders; 1999:668–673.
55. Hirshberg A, Dugas M, Banez EI, Scott BG, Wall MJ Jr, Mattox KL. Minimizing dilutional coagulopathy in exsanguinating hemorrhage: a computer simulation. *J Trauma*. 2003;54:454–463.
56. Lucas CE, Ledgerwood AM. Clinical significance of altered coagulation tests after massive transfusion for trauma. *Am Surg*. 1981;47:125–130.
57. Cinat ME, Wallace WC, Nastanski F, et al. Improved survival following massive transfusion in patients who have undergone trauma. *Arch Surg*. 1999;134:964–968, discussion 968–970.
58. Faringer PD, Mullins RJ, Johnson RL, Trunkey DD. Blood component supplementation during massive transfusion of AS-1 red cells in trauma patients. *J Trauma*. 1993;34:481–485, discussion 485–487.
59. Mitchell KJ, Moncure KE, Onyeije C, Rao MS, Siram S. Evaluation of massive volume replacement in the penetrating trauma patient. *J Natl Med Assoc*. 1994;86:926–929.
60. Martinowitz U, Zaarur M, Yaron BL, Blumenfeld A, Martonovits G. Treating traumatic bleeding in a combat setting: possible role of recombinant activated factor VII. *Mil Med*. 2004;169(Suppl):16–18, 4.
61. Rugeri L, Levrat A, David JS, et al. Diagnosis of early coagulation abnormalities in trauma patients by rotation thrombelastography. *J Thromb Haemost*. 2007;5:289–295.
62. Malone DL HJ, Fingerhut A. Massive transfusion practices around the globe and a suggestion for a common massive transfusion protocol. *J Trauma*. 2006;60:S91–S96.
63. Moore FA, Moore EE, Sauaia A. Blood transfusion. An independent risk factor for postinjury multiple organ failure. *Arch Surg*. 1997; 132:620–624, discussion 624–625.
64. MacLennan S, Williamson LM. Risks of fresh frozen plasma and platelets. *J Trauma*. 2006;60(Suppl):S46–S50.